

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:

KATZAROV S.A.
19, rue des Epinettes
CH-1227 Geneva
SWITZERLAND

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

02/11/2004

| | |
|---|---|
| Applicant's or agent's file reference 14 673/PCT | FOR FURTHER ACTION See paragraphs 1 and 4 below |
| International application No. PCT/IB2004/002165 | International filing date (day/month/year) 30/06/2004 |
| Applicant UNIVERSITE DE LAUSANNE | |

1. The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until **30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

| | |
|--|--|
| Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer Barbara Klaver |
|--|--|

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

21.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]: "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference 14673 / PCT | FOR FURTHER ACTION | |
| | see Form PCT/ISA/220 as well as, where applicable, item 5 below. | |
| International application No. PCT/IB2004/002165 | International filing date (day/month/year) 30/06/2004 | (Earliest) Priority Date (day/month/year) 30/06/2003 |
| Applicant <i>UNIVERSITE DE LAUSANNE</i> | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. **Certain claims were found unsearchable** (See Box II).

3. **Unity of invention is lacking** (see Box III).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regards to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. 2

as suggested by the applicant.

as selected by this Authority, because the applicant failed to suggest a figure.

as selected by this Authority, because this figure better characterizes the invention.

b. none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2004/002165

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
 - a. type of material
 - a sequence listing
 - table(s) related to the sequence listing
 - b. format of material
 - in written format
 - in computer readable form
 - c. time of filing/furnishing
 - contained in the international application as filed
 - filed together with the international application in computer readable form
 - furnished subsequently to this Authority for the purpose of search
2. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2004/002165

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/47 C12N15/12 A61K47/42 A61K38/17 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, Sequence Search, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|--------------------------------------|
| X | WO 94/03597 A (DUCHESNE MARC ; TOCQUE BRUNO (FR); RHONE POULENC RORER SA (FR); SCHWEI) 17 February 1994 (1994-02-17) claims; figures 1-3; examples 2,3; sequence 5 | 1-5, 10-22, 29-31 6-9 |
| X | & US 6 180 362 B1 (DUCHESNE MARC ET AL) 30 January 2001 (2001-01-30) claims; examples; sequence 6 ----- | 1-5, 10-22, 29-31 |
| X | WO 03/018630 A (FRENCH JULIET ; KENNEDY DEREK (AU); UNIV GRIFFITH (AU); HART DEREK (AU) 6 March 2003 (2003-03-06) page 50, line 23 – page 51, line 7; claims; figure 2; sequence 6 ----- -/- | 1-3, 10-12, 16-19, 21,29,31 |

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- °A° document defining the general state of the art which is not considered to be of particular relevance
- °E° earlier document but published on or after the international filing date
- °L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- °O° document referring to an oral disclosure, use, exhibition or other means
- °P° document published prior to the international filing date but later than the priority date claimed

- °T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- °X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- °Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- °&° document member of the same patent family

Date of the actual completion of the international search

21 October 2004

Date of mailing of the international search report

02/11/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Madruga, J

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2004/002165

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|---------------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| X | <p>DUCHESNE M ET AL: "Identification of the SH3 domain of GAP as an essential sequence for Ras_GAP-mediated signaling" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 259, 22 January 1993 (1993-01-22), pages 525-528, XP002092187 ISSN: 0036-8075 abstract; figure 2</p> <p>-----</p> | 1, 2, 10-16, 29, 31 |
| X | <p>YANG JIANG-YAN ET AL: "Antia apoptotic signaling generated by caspase-induced cleavage of RasGAP" MOLECULAR AND CELLULAR BIOLOGY, vol. 21, no. 16, August 2001 (2001-08), pages 5346-5358, XP002296743 ISSN: 0270-7306</p> <p>cited in the application</p> <p>page 5351, left-hand column, paragraph 2 - page 5352, right-hand column, paragraph 1; figures</p> <p>page 5354, left-hand column, paragraph 2 - right-hand column, paragraph 5</p> <p>-----</p> | 1, 2, 10-16, 26-31 |
| Y | <p>LEBLANC VERONIQUE ET AL: "Ras-GTPase activating protein inhibition specifically induces apoptosis of tumour cells" ONCOGENE, vol. 18, no. 34, August 1999 (1999-08), pages 4884-4889, XP002296744 ISSN: 0950-9232</p> <p>cited in the application</p> <p>the whole document</p> <p>-----</p> | 23-25 |
| Y | <p>SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1569-1572, XP002140133 ISSN: 0036-8075</p> <p>cited in the application</p> <p>the whole document</p> <p>-----</p> | 6-9 |
| A | <p>YANG JIANG-YAN ET AL: "A subset of caspase substrates functions as the Jekyll and Hyde of apoptosis." EUROPEAN CYTOKINE NETWORK, vol. 13, no. 4, December 2002 (2002-12), pages 404-406, XP008035485 ISSN: 1148-5493</p> <p>cited in the application</p> <p>the whole document</p> <p>-----</p> | |

INTERNATIONAL SEARCH REPORT

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|---|
| International Application No PCT/IB2004/002165 |
|---|

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|-----------------------|
| A | <p>YANG JIANG-YAN ET AL: "The RasGAP N-terminal fragment generated by caspase cleavage protects cells in a Ras/PI3K/Akt-dependent manner that does not rely on NFκB activation" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 277, no. 17, 26 April 2002 (2002-04-26), pages 14641-14646, XP002296745 ISSN: 0021-9258 cited in the application the whole document</p> <p>-----</p> | |
| A | <p>FELDMANN P ET AL: "control of growth and differentiation by drosophila rasgap, a homolog of p120 ras-gtpase-activating protein" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 19, no. 3, March 1999 (1999-03), pages 1928-1937, XP002255964 ISSN: 0270-7306 the whole document</p> <p>-----</p> | |
| A | <p>PRENDERGAST G C ET AL: "RAS REGULATORY INTERACTIONS: NOVEL TARGETS FOR ANTI-CANCER INTERVENTION" BIOESSAYS, CAMBRIDGE, GB, vol. 16, no. 3, March 1994 (1994-03), pages 187-191, XP001181926 ISSN: 0265-9247 the whole document</p> <p>-----</p> | |
| A | <p>WO 99/65947 A (KENIGSBERG MIREILLE ; DUCHESNE MARC (FR); BARLAT ISABELLE (FR); PARKER) 23 December 1999 (1999-12-23) cited in the application claims; examples</p> <p>-----</p> | |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2004/002165

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: 21-28
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB2004/002165

| Patent document cited in search report | | Publication date | | Patent family member(s) | | Publication date |
|--|----|------------------|--|--|--|--|
| WO 9403597 | A | 17-02-1994 | | FR 2694296 A1 CA 2141061 A1 EP 0652952 A1 WO 9403597 A1 JP 7509609 T US 6180362 B1 | | 04-02-1994 17-02-1994 17-05-1995 17-02-1994 26-10-1995 30-01-2001 |
| US 6180362 | B1 | 30-01-2001 | | FR 2694296 A1 CA 2141061 A1 EP 0652952 A1 WO 9403597 A1 JP 7509609 T | | 04-02-1994 17-02-1994 17-05-1995 17-02-1994 26-10-1995 |
| WO 03018630 | A | 06-03-2003 | | WO 03018630 A1 EP 1427754 A1 | | 06-03-2003 16-06-2004 |
| WO 9965947 | A | 23-12-1999 | | FR 2780062 A1 AU 764139 B2 AU 4151599 A CA 2331151 A1 CN 1305497 T EP 1087997 A2 WO 9965947 A2 HU 0103152 A2 JP 2002518001 T | | 24-12-1999 14-08-2003 05-01-2000 23-12-1999 25-07-2001 04-04-2001 23-12-1999 28-12-2001 25-06-2002 |

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION See paragraph 2 below

| | | |
|---|--|--|
| International application No. PCT/B2004/002165 | International filing date (day/month/year) 30.06.2004 | Priority date (day/month/year) 30.06.2003 |
|---|--|--|

International Patent Classification (IPC) or both national classification and IPC
C07K14/47, C12N15/12, A61K47/42, A61K38/17, A61P35/00

Applicant
UNIVERSITE DE LAUSANNE

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Madruga, J

Telephone No. +31 70 340-3121



Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002165

Box No. II Priority

1. The following document has not been furnished:

copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
 translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

the entire international application,
 claims Nos. 21-28

because:

the said international application, or the said claims Nos. with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the whole application or for said claims Nos.

the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

| | |
|----------------------------|---|
| the written form | <input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished <input type="checkbox"/> does not comply with the standard |

the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/002165

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---------------------|-------------|------------|
| Novelty (N) | Yes: Claims | 6-9 |
| | No: Claims | 1-5, 10-31 |
| Inventive step (IS) | Yes: Claims | |
| | No: Claims | 1-31 |

| | | |
|-------------------------------|-------------|-------------|
| Industrial applicability (IA) | Yes: Claims | 1-20, 29-31 |
| | No: Claims | |

2. Citations and explanations

see separate sheet

Re Item I

1. Sequence listing pages filed subsequently on 28.09.2004 do not form part of the application (Rule 13ter.1(f) PCT).

Re Item III.

2. Claims 21-28 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

3. The following documents are referred to in this communication:

D1 : WO 94/03597 A (DUCHESNE MARC ; TOCQUE BRUNO (FR); RHONE POULENC RORER SA (FR); SCHWEI) 17 February 1994 (1994-02-17)

D2 : WO 03/018630 A (FRENCH JULIET ; KENNEDY DEREK (AU); UNIV GRIFFITH (AU); HART DEREK (AU) 6 March 2003 (2003-03-06)

D3 : DUCHESNE M ET AL: "Identification of the SH3 domain of GAP as an essential sequence for Ras_GAP-mediated signaling" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 259, 22 January 1993 (1993-01-22), pages 525-528, XP002092187 ISSN: 0036-8075

D4 : YANG JIANG-YAN ET AL: "Antia apoptotic signaling generated by caspase-induced cleavage of RasGAP" MOLECULAR AND CELLULAR BIOLOGY, vol. 21, no. 16, August 2001 (2001-08), pages 5346-5358, XP002296743 ISSN: 0270-7306

D5: LEBLANC VERONIQUE ET AL: "Ras-GTPase activating protein inhibition specifically induces apoptosis of tumour cells" ONCOGENE, vol. 18, no. 34, August 1999 (1999-08), pages 4884-4889, XP002296744 ISSN: 0950-9232

D6: SCHWARZE S ET AL: "In vivo protein transduction: delivery of a biologically active protein into the mouse" SCIENCE, AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE,, US, vol. 285, no. 5433, 3 September 1999 (1999-09-03), pages 1569-1572, XP002140133 ISSN: 0036-8075

4. NOVELTY (Art. 33(2) PCT)

4.1 D1 discloses a peptide consisting of the sequence WMWVTNLRTD (P5, SEQ ID NO: 5), and peptides comprising the sequence WMWVTNLRTD (peptides P6 and P8) which are capable of inhibiting the transformation activity of the Ras protein (D1, example 3). D1 claims the use of said peptides in pharmaceutical compositions for the treatment of cancer. D1 discloses nucleic acid molecules encoding said peptides, vectors comprising said nucleic acids and host cells containing said peptide and said nucleic acid. Thus, the subject-matter of claims **1-5, 10-22, 29 and 31** is not new.

4.2 D2 discloses a peptide of 61 amino acids (D2, SEQ ID NO: 6, page 51, claim 22), which comprises the polypeptide encoded by SEQ ID NO: 4 of the present application (WMWVTNLRTD); said peptide is a mimetic which disrupts or prevents formation of a complex between the NTF2-like domain of G3BP-2 and an endogenous target peptide, for example rasGAP120; D2 claims the use thereof for breast cancer therapy (claim 34). Thus, the subject-matter of claims **1-3, 10-12, 14-19, 21, 29 and 31** is not new.

4.3 D3 discloses a peptide comprising amino acids 275-351 of RasGAP (comprising the SH3 domain) which has an effector function for signal transduction (see e.g figures 2, 3). Thus, the subject-matter of claims **1, 2, 10-12, 14-16, 29 and 31** is not new.

4.4 D4 discloses that a peptide consisting of amino acids 158 to 455 of RasGAP (N2 fragment, produced by RasGAP caspase cleavage), potentiates apoptosis and cell killing in genotoxin-treated HeLa cells (see page 5351, left-hand column, paragraph 2 to page 5354, right-hand column, paragraph 5, figures). HeLa cells are tumor cells. Thus, the subject-matter of claims **1, 2, 10-12, 14-16, 23-31** is not new.

4.5 The following observations have been taken into consideration for the assessment of novelty by the International Authority.

4.5.1 The activity to enhance the ability of a drug to kill cells is considered to be an inherent property of the peptides. Thus, any document disclosing a peptide as defined in the claims is regarded as novelty destroying for the product

claims directed to the peptide, even if the prior art document is silent about the activity of the peptide to enhance the ability of a drug to kill cells.

4.5.2 Optional or preferred features have no limiting effect on the scope of the claims (e.g. claims 16, 29; PCT Guidelines Part II-5.40).

4.6 The present application does not satisfy the criterion set forth in Article 33(2) PCT because the subject-matter of claims **1-5 and 10-31** is not new in respect of the prior art as defined in the regulations (Rule 64(1)-(3) PCT).

5. INVENTIVE STEP (Art. 33(3) PCT)

5.1 Dependent claims **6-9**, referring to a peptide according to present claim 1 conjugated to an agent which increases accumulation in the cell, said agent being preferably HIV-TAT ₄₈₋₅₇ peptide, do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step (Article 33(2) and (3) PCT) for the following reasons:

5.1.1 D1 is regarded as the closest prior art for these claims; D1 already suggests the conjugation of the peptides disclosed in D1 (e.g. P5) to improve the passage through the cell membranes and to increase the therapeutic efficacy (D1, page 3 lines 14-24).

5.1.2 Thus, the **problem** of improving the delivery of peptides derived from the N2 fragment of RasGAP to the cells, is **solved** in the application by conjugating said peptides to the HIV-TAT ₄₈₋₅₇ peptide.

5.1.3 A skilled person with knowledge of D6 would know that such a HIV-TAT ₄₈₋₅₇ peptide is suitable for this purpose and would combine the teachings of D1 and D6 to arrive to the subject-matter of present claims **6-9**.

5.1.4 It appears that other carriers might be used; the choice of one of them is considered as just one of several possibilities for a skilled person in view of a lack of any especial advantages or surprising properties which might justify an inventive step.

5.2 Thus, the present application does therefore not satisfy the criterion set forth in Article 33(3) PCT and the subject-matter of claims 6-9 does not involve an inventive step (Rule 65(1)(2) PCT).

6. INDUSTRIAL APPLICABILITY (Art. 33(4) PCT)

6.1 For the assessment of the present claims 21-28 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment (Rule 39.1(iv) PCT).

VIII Certain observations on the international application

7. The application does not meet the requirements of Article 6 PCT because claims are not clear for the following reasons:

7.1 Although the application discloses a peptide with homology to the WMWVTNLRTD sequence in the insect RasGAP protein (WLWVTAHRTG), no evidence is given that such a peptide also has the activity of enhancing the ability of a dog to kill cancer cells. No such evidence is given either for any of all the possible peptides (WxWVTxxRTx) other than for WMWVTNLRTD. Thus, subject-matter other than that concerning the peptides encoded by SEQ ID NOs: 1-4 (including WMWVTNLRTD) and to the peptide WLWVTAHRTG lacks support in the sense of Art. 6 PCT and does not seem to be sufficiently disclosed in the sense of Art. 5 PCT.

7.2 It appears from the description as a whole and in particular from table 2, that the presence of the sequence WMWVTNLRTD in the peptides claimed is an essential technical feature of the present invention. This essential technical feature is however not present in any of the independent claims. For these reasons the

claims lack clarity according to Art. 6 PCT taken in combination with Rule 6.3 (b) PCT (see also PCT Preliminary Examination Guidelines Part II 5.04-05).

7.3 In addition, due to the broad definition of the terms "fragments", "variants" and "part", the only technical feature remaining in the independent claims is the functional definition, namely that the peptide should enhance the ability of a drug to selectively kill cancer cells. This is considered to be a definition in terms of a result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result are however missing. Thus, all the independent claims do not meet the requirements of Article 6 PCT.